



MOC-CME Review

What do allergists in practice need to know about non-IgE-mediated food allergies



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Key Messages

- Non-IgE food allergic conditions have the ability to cause significant morbidity and are being increasingly recognized.
- Food protein–induced allergic proctocolitis (FPIAP) is a benign self-limited disorder that presents in otherwise healthy infants with bloody stools. Some centers are advocating observation without initial dietary intervention.
- Food protein enteropathy (FPE) is now an uncommon disorder that is often caused by a single food and associated with iron deficiency, hypoalbuminemia, and growth failure.
- Eosinophilic esophagitis (EoE) is a chronic disorder that can present at any age, and is treatable, but is associated with lower rates of self-resolution.
- Acute food protein–induced enterocolitis syndrome (FPIES) is often caused by a single food, usually not accompanied by fever nor by significant elevations in C-reactive protein, and overall has a good prognosis.
- Chronic FPIES is rare, has a similar clinical presentation to FPE, but is differentiated by the presence of acute FPIES when the food trigger is reintroduced after a brief period of exclusion.

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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize differences in clinical presentation and management among FPIAP, FPE and FPIES.
- Describe change in diagnostic criteria for eosinophilic esophagitis.

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

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Introduction

Unlike immunoglobulin (Ig) E-mediated food allergy (FA), in which 1 pathophysiological mechanism explains 1 disease process, non-IgE FA encapsulates a number of disease states caused by different mechanisms^{1,2} but unified in their ability to cause gastrointestinal inflammation. The commonest non-IgE-mediated disorders encountered and managed by allergists include food protein-induced allergic proctocolitis (FPIAP), eosinophilic esophagitis (EoE), food protein-induced enteropathy (FPE), and food protein-induced enterocolitis syndrome (FPIES). Knowledge of celiac disease (CD) is beyond the scope of this review, and is briefly discussed in supplementary section.

Non-IgE FA is increasing, particularly in children (the predominant group afflicted by these disorders).^{3,4} Although it has not been reported to cause fatality, non-IgE FA is capable of causing significant morbidity. Parents of children with FPIES report lower quality of life⁵ and experience greater difficulties in feeding compared with parents of children with IgE-mediated FA.⁶ Often non-IgE FA is poorly recognized, particularly in those with EoE and FPIES, leading to delays in diagnosis.^{7–9} This can result in unnecessary investigations, repeated hospital admissions, inappropriate therapies, increased risk of stricturing disease in EoE, and substantial health care costs.^{7,8,10} Some children with FPIES and EoE have concomitant IgE food allergies,⁸ adding to the burden of food elimination, and need for different action plans. Non-IgE FA has the potential to cause growth failure because of the underlying disease itself or from restricted intake; the cause of which can be multifactorial and may include food aversion, parental hesitation in introducing new foods, and implementation of overly restricted diets.^{11,12} Compounding matters further is the multitude of advice from social media platforms and diets downloadable from the Internet.

The keys of managing patients with non-IgE FA allergy are to provide an accurate diagnosis, and provide a plan that balances food avoidance with new food introduction. In more complex cases, in which multiple food triggers need to be avoided, regular medical and psychological support is required, preferably through a multidisciplinary clinic staffed by medical and allied health staff.

In this review, we discuss what allergists in practice need to know about non-IgE FA, discussing the clinical characteristics that differentiate non-IgE FAs from one another, and management principles. We focus on the 4 common non-IgE FAs: FPIAP, EoE, FPE, and FPIES. The clinical, laboratory, and endoscopic features of these disorders are summarized (Table 1).

Food Protein–Induced Allergic Proctocolitis

Food protein–induced allergic proctocolitis (FPIAP) is a benign self-limited disorder that affects young infants within the first few months of life.^{13–24} The prevalence of FPIAP is unknown. In a population-based prospective Israeli study, 0.16% of infants had rectal bleeding caused by cow's milk ingestion.²¹ In addition, in otherwise healthy infants who present with rectal bleeding, FPIAP is the cause in 60% of cases.²³

The diagnosis of FPIAP is made based on the history and presentation of a well-appearing, robust infant with streaks of blood and possibly mucus in stool.^{13–23} This is in contrast to an ill-appearing infant who appears in pain and has growth concerns (not FPIAP).²⁴ Thriving infants also are seen in between, with bouts of abdominal pain and times with more or less mucus or blood in stool. Most parents describe a gradual onset of symptoms that persist unless the offending food is removed. In a cohort of 95 children with food protein colitis, 25% had abdominal pain and 5% had diarrhea at presentation.¹³ In a Finnish cohort, 70% of infants had bloody diarrhea, 25% blood in stool only, 5% diarrhea only, 18% vomiting, and 10% growth concerns.²⁰ In summary, most babies

Table 1

Proposed Diagnostic Criteria for Patients Presenting with Acute FPIES in the Community Setting from the International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome^{a,62}

Major criterion	Minor criteria (3 or more)
Vomiting (1–4 hours after ingestion of the suspect food) and absence of classic IgE-mediated allergic skin or respiratory symptoms	• A second (or more) episode of repetitive vomiting after eating the same suspect food • Repetitive vomiting episode 1–4 hours after eating a different food • Extreme lethargy with any suspected reaction • Marked pallor with any suspected reaction • Need for emergency department visit with any suspected reaction • Need for intravenous fluid support with any suspected reaction • Diarrhea in 24 hours (usually 5–10 hours) • Hypotension • Hypothermia

Abbreviations: FPIES, food protein–induced enterocolitis syndrome; IgE, immunoglobulin E.

^aThe diagnosis of acute FPIES reactions requires the major criterion and 3 or more of the minor criteria. If only a single FPIES reaction has occurred, it is strongly recommended that a diagnostic food challenge is performed. Although not part of the criteria, recovery within a few hours is typical for FPIES but atypical for gastroenteritis/sepsis.

with FPIAP have normal growth. If over time the child develops growth or other gastrointestinal concerns, an alternative diagnosis should be explored.

Results of a physical examination are often normal, although one should pay close attention to the growth chart (monitoring percentiles) and the presence or absence of an anal fissure. A history of either constipation or recent acute diarrhea in an otherwise well infant should increase suspicion for a fissure.²⁴ In addition, routine testing for occult blood in fussy infants is not recommended.

No laboratory studies (blood or stool) confirm the diagnosis of FPIAP. Stool cultures or polymerase chain reaction studies may be performed to assess for underlying infection if clinically indicated.²⁴ Results of a complete blood count, if obtained, often are normal, although a few may develop mild iron-deficiency anemia.^{13,16,23} Sigmoidoscopy (which is not required for diagnosis) shows increased eosinophils and lymphoid nodular hyperplasia.^{15,17}

In the acute severe setting, which is rare, infants are often seen in an emergency department and admitted for evaluation. The differential diagnosis is extensive: intussusception, Meckel diverticulum, infectious colitis, necrotizing enterocolitis, inflammatory bowel disease, and concomitant underlying primary immunodeficiency.²⁴ Although an infant would be unlikely to be brought directly to the allergist's office, knowledge of differential diagnoses is essential.

Management involves removing the causal food protein. As with other non-IgE-mediated FA disorders, identification of the causative food by FA testing remains challenging. Allergy skin prick testing or serum specific IgE (ssIgE) testing for foods are usually negative, and a negative test does not rule out FPIAP.^{14,16,19} Positive testing would allow for a more cautious introduction of food(s) because a few reported infants developed IgE-mediated reactions with reintroduction.^{14,16,25}

Infants with FPIAP's conditions improve with dietary restriction. Because up to 60% of affected infants are breastfed and thus up to 40% of infants are formula fed, both breastfeeding mothers and infants remove food, which results in improvement in symptoms.^{13–19,23} Cow's milk is the most common cause of FPIAP

in most series.^{15,19,23} In a Turkish study, 100% of infants had improvement with dietary restrictions: 83% milk alone, 14% milk and another food, and 3% milk and more than 2 additional foods.¹⁴ Other foods implicated include soy, eggs, wheat, chicken, corn, other grains, or fish, although how aggressive one needs to be in avoiding other foods in an otherwise healthy infant remains controversial.^{13,15,20} Approximately 10% of infants may require elemental formula.

Within 72 hours after dietary changes, resolution of symptoms (visible blood) should be seen in most patients, although symptoms may last a week in those more symptomatic initially.^{16,19} Hemocult testing may stay positive longer. For bottle-fed infants, 80% of patients respond to extensively hydrolyzed formula (EHF), with the remainder responding to amino acid–based formula (AAF).¹⁴ In a breastfed infant, most mothers will remove milk or milk/soy, although further restrictions may be necessary.^{14,18} Removal of food(s) may require consultation with a dietician, who will ensure healthy diets for both mother and infant.

Recently, a few groups have recommended removal of the suspected food for a month, with reintroduction (as long as testing is negative).^{16,20,21,25} If symptoms develop, one would remove the food again, and the diagnosis of FPIAP would be confirmed, and longer avoidance would be necessary.^{16,20,21,25} If asymptomatic, infant and mother may continue to ingest the previously suspected trigger. Twenty percent of breastfed infants with FPIAP are thought to have spontaneous remission without maternal dietary elimination.^{16,25} Recently, 21 parents whose infant's symptoms cleared with milk elimination were asked to reintroduce it a few months later. Of the 14 infants who were challenged, 11 tolerated reintroduction, 1 had rectal bleeding, and 2 had nonbloody diarrhea.²¹

Since then, Sopo and colleagues²⁵ published a proposal for management of FPIAP in which symptomatic well-appearing infants are observed for 1 month.²⁵ If there is not spontaneous resolution, the authors recommend avoidance of cow's milk for a week, along with baseline hemoglobin. Based on response to diet elimination and presence or absence of anemia, a flow diagram has been developed.²⁵

Most infants will outgrow FPIAP by a year of age without sequelae and are able to ingest the food without restriction. In a Turkish cohort of 60 infants, 53% outgrew FPIAP by a year of age and 80% by 2 years of age. For those older than 2 years, milk remained a culprit.¹⁴ Two studies followed up with infants until they were 10 years of age, and none developed chronic inflammatory bowel disease.^{13,26} More recently, a few studies have identified cow's milk FPIAP in infancy as a risk factor for later development of functional gastrointestinal disorders in children.^{27,28} Additional studies are needed to follow up with these infants long term.

Food Protein Enteropathy

Food protein enteropathy is a pediatric disease, with infants presenting within a few weeks of either cow's milk/soy formula or solid foods introduction. The prevalence of the disease is unclear, but it appears to be decreasing. In 1 study, FPE presented to 1 institution at an average rate of 3 patients per year between 1962 and 1972, but by the 1990s, only a total of 5 patients were diagnosed with FPE.²⁹ This may be attributable to increased rates of breastfeeding and better recognition with prompt formula/food elimination, leading to milder phenotypes not requiring allergist or hospital intervention.³⁰

The cardinal feature of FPE is nonbloody persistent diarrhea, and associated features may include intermittent vomiting, hypoalbuminemia, anemia, and increased fecal fat excretion.^{1,30} Unlike FPIES and FPIAP, FPE is not reported in exclusively breastfed infants. Symptoms appear within weeks of introduction of a food trigger. Cow's milk and soy are the commonest triggers, but other reported

causative foods include typical FPIES foods such as rice, egg, poultry, fish, and shellfish.^{29,31}

Endoscopy is important to confirm a diagnosis of FPE, given the myriad of other conditions that present with persistent diarrhea. Typical findings include lymphonodular hyperplasia, villous atrophy, and increased number of intraepithelial cells.¹

Management is relatively straightforward, involving elimination of the causal food, which should result in disease resolution in a matter of weeks. In cases of cow's milk or soy FPE, EHF remains the most appropriate formula choice, but if significant failure to thrive exists, then one should consider commencing an AAF.³² Infants should then be rechallenged after 12 months of age, with most cases having resolved by 1 to 3 years of age.^{33,34}

Eosinophilic Esophagitis

The most common eosinophilic gastrointestinal disease, reported in all continents, is EoE, with an estimated prevalence of 1/2000.³⁵ Although EoE has been initially regarded as a mixed non-IgE/IgE disorder, EoE could in fact be an IgG4-associated disease, given the presence of IgG4 plasma cells within the esophageal submucosa, which disappear with swallow corticosteroids,³⁶ the apparent lack of benefit skin prick testing/sslIgE is in ascertaining food triggers,³⁷ and the lack of response of the disorder to anti-IgE monoclonal therapy.³⁸

Patients with EoE are diagnosed at any age and at any time; however, their presentations vary per age. Infants and toddlers present with gastroesophageal reflux (either difficult to treat or inability to wean medications), vomiting, feeding difficulties, growth concerns, and irritability. School-age children describe heartburn, regurgitation, vomiting, and abdominal pain. Adolescents and adults typically present with dysphagia and food or pill impaction, although chest pain, abdominal pain, and heartburn may occur.^{39–42} Patients may compensate for their symptoms by drinking a lot with meals, eating slowly, or cutting food into small pieces. At diagnosis, patients may be underweight, overweight, or normal in size.⁴³

Because many patients have concomitant atopy (IgE-mediated food allergy, asthma, allergic rhinitis, or eczema),^{39–42} the allergist may be the one who suspects the diagnosis and refers for evaluation. Other times, a patient has been diagnosed and is referred to an allergist.

International consensus guidelines have been published in 2007, 2011, and most recently in 2018.^{35,40,44,45} In 2011, patients met criteria for having eosinophilic esophagitis as long as they had symptoms of esophageal dysfunction, increased eosinophils noted only in the esophagus (≥ 15 intraepithelial eosinophils/high-power field), and gastroesophageal reflux disease (GERD) was ruled out by treatment with high-dose proton pump inhibitor (PPI).^{39,46} The most recent consensus guidelines, published in 2018, removed prior treatment with PPI as a mandatory requirement, and having symptoms and increased eosinophils in the esophagus (≥ 15 intraepithelial eosinophils/high-power field) as diagnostic.^{35,46} Nevertheless clinicians still may elect a trial of PPI to determine whether the child has PPI-responsive EoE. Furthermore, patients can have both EoE and GERD concomitantly. Gastroesophageal reflux disease may lead to EoE by damaging esophageal epithelium and increasing antigen exposure, and EoE may lead to GERD by decreasing motility.³⁵ Patients also may have pollen-induced EoE, food-induced EoE, or a combination. Patients with EoE, no matter the trigger, are at increased risk for fibrosis, endothelial dysfunction, or stricture.³⁵

The goals of treatment for EoE include symptom resolution and elimination of eosinophils. Therapies include dilations (on occasion), diet, or medication. Histologic evaluation is required to determine success of therapy.

Table 2
Epidemiological, Clinical, Laboratory Features and Management of FPIAP, FPE, EoE, and Acute FPIES

	FPIAP	FPE	EoE	Acute FPIES
Age at onset	1 day–6 months (usually within first 4 weeks of life)	Up to 2 years of age	Toddler-adulthood	Typically 1 day–1 year (may be older, in cases of fish, chicken, or egg FPIES)
Food proteins implicated				
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk, wheat, soy, egg	Cow's milk, soy, grains, egg
Less common	Egg, corn	Wheat, egg, rice, seafood	Nuts, seafood, fruit, vegetables	Meats, seafood, nuts, fruit, vegetables
Multiple food hypersensitivities	20% both cow's milk and soy	Rare	Milk and wheat are most common	~25% cases
Feeding at the time of onset	Formula or exclusive breastfeeding	Formula or solids	Full diet	Formula, solids, and uncommonly in exclusively breastfed
Atopic background				
Family history of atopy	Up to 25%	Unknown	30%	40%-70%
Personal history of atopy	Up to 20%	22%	80%	30%
Symptoms				
Emesis	No	Intermittent	Moderate	Prominent and profuse
Diarrhea	No	Moderate	Rare	~35% cases (usually within 24 hours)
Bloody stools	Moderate	Rare	No	Rare
Edema	No	Moderate	No	No
Shock	No	Absent	No	~Up to 15%
Failure to thrive	No	Moderate	Minimal	No
Dysphagia	No	No	Intermittent	No
Laboratory findings				
Anemia	Mild	Moderate	No	No
Hypoalbuminemia	Rare	Moderate	No	No
Methemoglobinemia	No	No	No	May be present
Acidemia	No	No	No	May be present
Allergy evaluation				
Food prick skin test	Negative	Negative	Occasionally positive	Usually negative
Serum food-allergen IgE	Negative	Negative	May be helpful for milk	Usually negative
Peripheral blood eosinophilia	Occasional	No	May be present, but cannot be used as marker for EoE	No
Biopsy findings				
Villous injury	No	Variable	No	Patchy, variable
Colitis	Focal	Absent	No	No
Mucosal erosions	Occasional, linear	Absent	No	No
Lymphoid nodular hyperplasia	Common	Yes	No	No
Eosinophils	Prominent	Few	Yes	May be present
Treatment	Options include no treatment and observe; removal causal food from maternal diet, or hypoallergenic formula. Some centers re-challenge within a month.	Removal of causal food; symptoms clear within 1-3 weeks. Re-challenge by 1-3 years of age.	Directed diet elimination Elemental diet Swallowed steroids Dilations	Removal of causal food. Rechallenge 12 months after last reaction (although fish FPIES may wish to challenge when > 5 years of age)
Natural history	Resolved by 9-12 months	Majority outgrow by 1-3 years of age	Rare to outgrow	Most outgrown by 2-3 years of age

Abbreviations: EoE, eosinophilic esophagitis; FPE, food protein enteropathy; FPIAP, Food protein–induced allergic proctocolitis; FPIES, food protein–induced enterocolitis syndrome; IgE, immunoglobulin E. Modified from Nowak-Węgrzyn¹⁶ and Cheng.⁷⁷

- Esophageal dilation: Esophageal dilation has been performed either separately or in combination with other therapies. Side effects include esophageal tear or chest pain in a minority of patients.⁴⁷ Therapy is not curative, and patients tend to develop recurrence of symptoms, fibrosis, and stenosis.⁴⁷
- Dietary therapy: In almost all patients with EoE, food is a trigger.^{35,39–43} When food is removed, symptoms improve and biopsy results normalize, and when suspected foods are reintroduced, symptoms recur and biopsy results worsen.

Diet elimination may be directed based on allergy testing (skin test and patch test), food removal based on patient's diet and most likely food trigger, or removal of foods based on 2-food, 4-food, or 6-food elimination, or a total elimination diet with elemental formula.^{39–44,46,48–51} Elemental formula alone has the best chance of inducing remission (~90%), compared with the 6-food elimination diet (50%–70% chance of remission). Targeted food elimination based on skin prick and patch testing has a similar efficacy to the 6-food elimination diet.⁵² Although food patch testing is not difficult to perform, a lack of standardization remains as well as potential wide variation in accuracy and reproducibility.⁵³ Compliance with dietary restrictions is difficult, particularly in the older children and adolescents, in whom avoidance of multiple staple foods or reliance on a formula alone is usually not practical or sustainable. Options for the dietary elimination of foods include a “step-up” approach, in which foods are progressively removed until normalization of biopsy results, or a “step-down” strategy, in which many foods are removed, scope is normalized, and then, over time, foods are added back.^{46,51} For patients on dietary therapy, a referral to a nutritionist is recommended because compliance is important.⁴³ Removal of the correct food is curative; however, side effects may include poor growth, nutrient deficiency, and difficulty following diet restriction(s).^{35,39–43,46,48–51}

- Medication: The first successful medical therapy for EoE was systemic steroids, although side effects preclude their use long term.^{39,40} Short bursts may be used to induce remission quickly in symptomatic patients.⁴⁰ Swallowed steroids have become the mainstay for medical therapy,^{46,54–57} although there is some hope for biologics in the future.⁵⁸ Nebulized budesonide (made into slurry) or aerosolized fluticasone (or other inhaled steroids without a spacer) induces remission in 50% to 80% of patients.^{54–57,59} Esophageal candidiasis, adrenal suppression, growth concerns, and bone loss may occur in susceptible patients, although in many the advantage is that most do not require diet restriction.^{39,40,42,55–57} Combination therapies (PPI, swallowed steroids, food restrictions) also have been used with success, depending on the needs of the individual patient.⁶⁰

Unlike other non-IgE-mediated food allergies, only 5% of pediatric patients were found to outgrow the condition over time.⁶¹ Eosinophilic esophagitis is considered a chronic disorder that is treatable.

Food Protein–Induced Enterocolitis Syndrome

Food protein–induced enterocolitis syndrome is predominately a pediatric disorder, with most children presenting by 4 to 6 months of age, corresponding to the time of formula or solid food introduction. Overall the commonest triggers tend to be cow's milk, soy, egg, and grains (particularly rice and oats).⁸

Food protein–induced enterocolitis syndrome has 2 recognized phenotypes, acute and chronic. Acute FPIES is more common, and it is characterized by profuse, repetitive vomiting, usually 2 to 4 hours after ingestion of the triggering food protein. Associated clinical features may include floppiness, pallor, and lethargy. Hypotension (shock), hypothermia, neutrophilia, thrombocytosis, and

a metabolic acidosis have all been described as potential co-associated features.^{1,7,62} Prevalence estimates of acute FPIES based on prospective population studies varies from 15 per 100,000 infants younger than 2 years of age per year in an Australian study,⁸ 3 per 1000 cases of cow's milk FPIES in a single-center Israel birth cohort,⁶³ and 7 per 1000 cases of FPIES in a recent Spanish single-center birth cohort.⁶⁴ Likely Australian data represent an underestimate of true cases, given that the study was based on voluntary reporting of new cases by pediatricians/allergists, and less severe cases may not have been captured.⁸ The prevalence of acute FPIES appears to be increasing; this is likely in part to be attributable to improved recognition by both the lay and medical communities.³

Chronic FPIES is rare. Reports of FPIES in the 1960s to 1970s originally described this phenotype, which occurred only in neonates and young infants.^{65,66} Chronic FPIES has only been caused by continuous exposure to cow's milk or soy protein.^{65,66} It is associated with persistent vomiting or diarrhea, growth failure, anemia, or hypoalbuminaemia.^{1,65–67} Thus it is clinically indistinguishable from FPE and necrotizing enterocolitis (NEC). But unlike FPE or NEC, early reintroduction of the food trigger in chronic FPIES induces an acute FPIES reaction.^{65,66} Signs suggestive of NEC over chronic FPIES include presence of an elevated C-reactive protein (CRP), thrombocytopenia, and leukopenia.⁶⁸ The endoscopic features of chronic FPIES remain poorly studied. The only published endoscopic reports of chronic FPIES come from the 1960s, in which only a sigmoidoscopy was performed, and in all patients rectal biopsy specimens showed mixed inflammatory infiltrate (lymphocytes, plasma cells, neutrophils), with epithelium destruction, crypt abscesses, and rectal gland distortion.⁶⁶

More is now known about the immune pathophysiology of acute FPIES. Whereas previously it was postulated to be a T-cell–mediated disorder, 2 recent studies have highlighted the importance of innate immune system activation.⁶⁹ Further work is required to determine which specific signal pathways are involved.

Allergists must be able to confirm the diagnosis of FPIES. The diagnosis remains a clinical one. Recently published international consensus guidelines suggest a more rigorous approach to diagnosis of acute FPIES, introducing a system of major and minor criteria (Table 2),⁶⁷ which are particularly helpful to those conducting research in FPIES. No such specific criteria exist for chronic FPIES. In essence, the criteria ensure that those presenting once with profuse vomiting or with mild reactions (eg, vomiting and pallor alone) are not inappropriately diagnosed. The criteria strongly encourage a diagnostic oral food challenge (OFC) in those with a single reaction (even if they fulfill the diagnostic criteria from 1 reaction). However, the accuracy of these criteria has not been evaluated, and it is based on expert opinion. Clinical accrual should prevail; clinicians could argue that an OFC is not required in an infant who presents 2 hours after eating rice for the first time with profuse vomiting, lethargy, and floppiness, and who completely recovers within a few hours.

Recently, Lee et al⁷⁰ compared acute FPIES reactions presenting to the emergency department with children presenting with vomiting and subsequently diagnosed with infectious gastroenteritis and sepsis.⁷⁰ They concluded that floppiness, pallor without fever, and a normal CRP should alert clinicians to the diagnosis of FPIES, whereas an alternative diagnosis must be considered in those presenting with an elevated CRP (with no cases of acute FPIES in their cohort presenting with a CRP value > 20 mg/dL).⁷⁰ Allergists should be aware that febrile FPIES has been reported.⁷¹ However, this phenotype appears to be rare outside of Asia. Why this is the case is unclear, but it highlights the possibility of genotype-phenotype differences. Lee et al⁷⁰ also reported that children with FPIES were likely to be admitted for a shorter time, and thus recovered faster than those with sepsis and gastroenteritis.⁷⁰ Symptom resolution within hours,

despite not being part of the diagnostic criteria, should alert the clinician to a potential diagnosis of FPIES.

Allergists must consider differential diagnoses in those presumed to have FPIES. Acute FPIES may be misdiagnosed as sepsis, gastroenteritis, and a surgical abdominal emergency.^{67,70} Metabolic syndromes, multiple food protein intolerance, immunodeficiency/dysregulation syndromes, and early-onset inflammatory bowel disease⁶⁷ must be considered in those who have co-associated features, such as failure to thrive, persistent diarrhea despite appropriate food elimination, elevated inflammatory markers, and reactions to multiple different food proteins only settling with an AAF.

Allergists should be aware that one does not have to wait until a child is 3 years or older to perform an OFC to ascertain tolerance. Although no study has systemically challenged children at regular intervals, many children do outgrow FPIES faster than previously appreciated. Rates of tolerance to rice and cow's milk by 24 months of age were reported in 1 Australian study to be as high as 63% (87% by 36 months) and 56% (88% by 36 months of age).⁷² Similar figures for cow's milk tolerance have been reported in Israeli⁶³ and Korean cohorts,⁷³ but lower rates of tolerance are often reported from US cohorts.⁶² Proportion tolerant to egg by 36 months of age was low in 1 study (12.5%; $n = 8$)⁷² but higher in another study ($\sim 50\%$; $n = 8$).⁷⁴ Presence of low-level IgE sensitization to the triggering food⁶² and children with fish FPIES⁷² appear to be associated with lower rates of tolerance, but such factors should not preclude children undergoing OFCs. In 2 studies, a small proportion of children with fish FPIES were tolerant at 36 months of age (12.5% in 1 study, $n = 4$ ⁷²; and $\sim 20\%$ in another study, $n = 44$ ⁷⁴), but this increased to 75% by 5 years in the study with the larger number of fish FPIES cases.⁷⁴ Thus the allergist may wish to challenge those to fish by at least 5 years of age, but consider challenging those with rice, cow's milk, and egg at a much earlier age.

Oral food challenges should be conducted in hospital, given that the safety of home challenges has not been evaluated. How these are conducted will vary between centers, but the following tenants should be observed: (a) the patient is observed for at least 4–6 hours and an age-appropriate dose is eaten (whether this is given as a single dose or as split doses)⁷⁵; (b) for determination of tolerance an sIgE or skin prick test should be considered at the time of the OFC (particularly to cow's milk and in the authors' experiences egg) because of the risk of IgE-mediated transformation⁶²; (c) intravenous access either should be performed before a challenge (particularly for a diagnostic OFC) or at least should be readily available; and (d) ondansetron (oral, intravenous, intramuscular) is effective in some patients, reducing the severity and frequency of vomiting during an acute reaction,⁷⁶ but because of its potential to prolong QT intervals, it should not be given to those with heart defects or a history of arrhythmias. The safety of ondansetron in infants younger than 6 months of age has not been evaluated.⁷⁷

Allergists should provide reassurance that most children (approximately 75%) will only have 1 trigger, that avoidance of foods with precautionary labeling is not required, and that exclusion of the food trigger in the maternal diet while breastfeeding is not necessary unless the child is symptomatic (which may not present as persistent vomiting, but rather as irritability, diarrhea, and significant difficulty in settling).^{8,67}

Dietary guidelines are available to assist in new food introduction. In essence they promote the introduction of foods less likely to cause FPIES first before more common FPIES triggers are tried (eg, sweet potato, banana, legumes, dairy, soy, egg, rice, oats, chicken, and fish).⁶⁷ Triggers vary per region. Although these are based on expert opinion, they at least promote new food introduction and provide a framework for parents to follow, who are often worried about trying new foods for their child. Knowledge of the following will also assist allergists in advising food introduction.

- In infants with cow's milk FPIES, if a formula is required, then EHF is the first choice (10%–20% co-reactivity) over soy (40%–60% co-reactivity)⁸; AAFs are appropriate in those who react to EHF.³²
- Most children with rice FPIES can tolerate corn (1% co-reactivity) and wheat (5% co-reactivity) but appear to be at higher risk of reacting to oats (40% co-reactivity); presumably because of the closer taxonomic relationship between rice and oats.⁷⁸
- Those with chicken FPIES must avoid all poultry.
- Although sporadic reports have been made of some children with egg, cow's milk, and fish FPIES, being tolerant to baked egg, baked milk, and tinned fish, respectively, this has not been systematically examined, and such challenges should be done under medical observation.^{67,79}
- Children reacting to vegetables or fruits are at greater risk of multiple food FPIES (>3 foods) and are more likely to have concomitant FPIES to grains.⁷⁹
- Little is known about fish FPIES. Sopo et al⁸⁰ reported that of 57 cases of fish FPIES, 37 reacted to a single species (although 22 had not eaten another species of fish).⁸⁰ Current advice is to avoid all fish, or if there is a desire to eat a new fish species, then a medically supervised OFC should be done.
- The proportion of children with fish FPIES who co-react to shellfish remains unclear.
- Adult-onset FPIES has been reported, and it differs from childhood-onset FPIES, with most having previously had a prolonged period of tolerance, and the main causative foods are fish, shellfish, and wheat.⁸¹

Allergists must provide parents with a written FPIES emergency plan in case of future reactions. In some countries, standardized action plans for childcare centers and schools are also available. Adrenaline auto-injectors are not required for those with FPIES alone, although some parents may choose to carry ondansetron wafers (particularly if they are traveling).

Conclusion

Although non-IgE FAs are less common than IgE FA, the prevalence of some non-IgE FA disorders is increasing. They can cause psychological distress, nutritional failure, and significant health care burden because of their greater potential to cause multi-food avoidance, food aversion, misdiagnosis, and sometimes the need for repeated endoscopic evaluation. Allergists must rapidly provide an accurate diagnosis, therapy plan, and reassurance that for most non-IgE FA (eg, FPIES, FPE, FPIAP) the prognosis is excellent. In more complex cases, having a multidisciplinary clinic approach with input from dietitians, speech pathologists, and medical staff (allergists and gastroenterologists) is more constructive, collaborative, and practical than the allergist trying to manage such patients on their own.

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[eSupplement]

Patients may present to allergists with gastrointestinal symptoms for which they want allergy testing. They also may present with thoughts that they have a gluten sensitivity. Unlike patients with IgE-mediated reactions to wheat in which skin testing is helpful, allergy testing for celiac disease (CD) or gluten sensitivity is not. The scope of this review article does not permit an extensive review of CD or gluten sensitivity or the difference between the 2. However, knowledge about the presentation, diagnosis, and treatment of patients with CD is important, because delay in diagnosis leads to a variety of adverse health effects, including persistent symptoms, anemia, poor growth, autoimmune disease, and cancer.^{1–6} Early diagnosis, especially in childhood, is also associated with an overall better prognosis.²

Celiac disease affects approximately 1% of the worldwide population.^{1–6} Failure to thrive and chronic diarrhea are seen most

often. Patients also may present with a variety of gastrointestinal and nongastrointestinal symptoms, including abdominal pain, constipation, bloating, oral ulcers, rashes (dermatitis herpetiformis), osteoporosis, anemia (iron or folate deficiency), weight loss, fatigue, fertility concerns, and/or anxiety.^{1–6} Some patients who are at higher risk of developing CD are asymptomatic when diagnosed. Having a first-degree relative with CD, type I diabetes mellitus, autoimmune thyroid disease, Down syndrome, Turner syndrome, IgA nephropathy, IgA deficiency, or other autoimmune disorders puts one at higher risk.³ If suspicious, allergists can certainly order screening serologic tests before referral to the GI department. For accurate interpretation, patients must have gluten in their diet for at least a month before obtaining study.⁵ Laboratory work should include total IgA level along with IgA antibodies to endomysium (EMA) and human tissue transglutaminase (tTGA).^{1–6} Endomysium has a high sensitivity and high specificity. However, the tissue transglutaminase antibody (tTG) is the universally recommended screening test. In children younger than 5 years of age, IgA- or IgG-based deamidated gliadin antibody testing is used.^{3,5} If evidence of IgA deficiency is seen, testing with the tTG-IgG is recommended. Most patients with celiac disease are HLA-DQ2 or HLA-DQ8 positive (therefore, if a patient is not ingesting gluten and has negative HLA testing, the result is less likely to be CD).^{1–6} However, many people are HLA-DQ2 or HLA-DQ8 positive and never develop the disease. Diagnosis is often confirmed with duodenal biopsy.⁵ Once diagnosed, patients must be educated and maintain strict avoidance of all forms of gluten.^{1–6} Referral to a nutritionist is often necessary.

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